SYNOPSIS

NAME OF SPONSOR/COMPANY: The R.W. Johnson Pharmaceutical Research Institute NAME OF FINISHED PRODUCT: TOPAMAX® (topiramate) tablet NAME OF ACTIVE INGREDIENT(S): 2,3:4,5-bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER @@7000fad8004b3c3	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: CR005455 Ti**tle of Study**: Topiramate (RWJ-17021-000) Clinical Trial in Primary Generalized Tonic-Clonic Seizures		
Investigators: 18 investigators		
Study Centres: 18 study centers		
Publication (Reference): None		
Studied Period (years): 5 May 1994 - 5 July 1996		**Phase of development**: 3
Objectives: This trial was designed to evaluate the safety and efficacy of oral topiramate as adjunctive therapy in subjects with uncontrolled primary generalized tonic-clonic (PGTC) seizures (i.e., tonic-clonic seizures considered to be generalized from the onset) with or without other generalized seizure subtypes.		
Methodology: This was a multicenter, randomized, double-blind, placebo-controlled trial that evaluated topiramate total daily (target) dosages of 175, 225, or 400 mg/day based on subject's weight to approximate 6 mg/kg/day (theoretical range: ≤9.3 mg/kg/day) as adjunctive therapy in subjects with PGTC seizures with or without other generalized seizure subtypes. The trial included a baseline phase (approximately 56 days in duration) and a double-blind phase (approximately 140 days in duration). During the baseline phase, the number and type of seizures that occurred were monitored while subjects received a constant dosage of one or two antiepileptic drugs (AEDs). Those subjects who were eligible for the double-blind phase of the trial were randomized in equal proportions at each center to receive either placebo or topiramate while continuing on their background AED regimen. Efficacy was evaluated based on the reduction from baseline in average monthly PGTC seizure rate, the primary efficacy variable, and on the reduction from baseline in average monthly seizure rate based on all seizures. Efficacy was also evaluated by the percent of treatment responders (subjects with a ≥50% reduction in average monthly seizure rate) based on PGTC seizures and based on all seizures, and subject's global evaluation of improvement in seizure severity. Safety was evaluated by reported adverse events, clinical laboratory tests, vital sign and body weight measurements, electrocardiograms (ECGs), physical examinations, and neurologic examinations. Subjects (or their parents/legal guardians) completed evaluations on mental status including level of alertness, level of interaction with their environment, ability to perform activities of daily living, and responsiveness to verbal requests. In addition, plasma AED concentrations were measured at periodic intervals to assess potential effects of topiramate on background AEDs.		
Number of Subjects (planned and analyzed): Eighty subjects were enrolled; 41 were randomly assigned to receive placebo and 39 were randomly assigned to receive topiramate. All 80 subjects were included in the intent-to-treat analyses of efficacy and safety.		
Diagnosis and Main Criteria for Inclusion: Subjects (≥ 4 years of age; ≥25 kg) enrolled in the trial had PGTC seizures with or without other generalized seizure subtypes. Subjects were to have three or more PGTC seizures during the 56-day baseline phase (with at least one during each 28-day period) while on a stable regimen of one or two AEDs.		
Test Product, Dose and Mode of Administration, Batch No.: Topiramate was supplied as white 25 mg (R5489) and yellow 100 mg (R5509) tablets. Maximum dosages of topiramate based on subjects' weight were 175 mg/day (25 to 33.9 kg), 225 mg/day (34 to 42.9 kg), 400 mg/day (≥43 kg).		
Duration of Treatment: The total duration of double-blind therapy was 140 days, including a 56-day titration period and an 84-day stabilization period.		
Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied as "25 mg" (R5721) and "100 mg" (R4567) tablets to match topiramate tablets.		
Criteria for Evaluation: Efficacy: The efficacy of topiramate in the treatment of PGTC seizures was based on a statistically significant between-group difference with respect to percent reduction in average monthly PGTC seizure rate. Safety: Safety was evaluated by reported adverse events, clinical laboratory tests, vital sign and body weight measurements, ECGs, physical and neurologic examinations, and evaluations of the subject's mental status.		

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Statistical Methods: A two-way (with treatment and center as factors) analysis of variance on ranks was used to analyze treatment group differences in percent reduction from baseline seizure rate for both PGTC seizures and all seizures. An additional efficacy assessment compared treatment groups with respect to percent of PGTC responders and responders based on all seizures, stratified by center, using the Cochran-Mantel-Haenszel method. The global evaluation of improvement in seizure severity was analyzed by exact Wilcoxon rank-sum tests stratified by center and unstratified.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: Topiramate was statistically superior to placebo with respect to percent reduction in average monthly seizure rate and percent treatment responders for both PGTC seizures and all seizures combined (Table 1) . The percent reduction from baseline in average monthly seizure rate numerically favored topiramate over placebo for absence (53% vs. 4%), myoclonic (52% vs. an increase of 401%), and tonic (16% vs. an increase of 1%) seizures.

Table 1: Summary of the Efficacy Results for the Double-Blind Phase
(All Randomized Subjects; Protocol CR005455)

Efficacy Assessment	Placebo	Topiramate	p-value
Primary Variable			
Percent reduction from baseline in average monthly seizure rate for PGTC seizures	9.0	56.7	0.019[b]
Secondary Variables			
Percent reduction from baseline in average monthly seizure rate for all seizures	0.9	42.1	0.003[b]
Percent treatment responders[a]:			
PGTC seizures	20	56	0.001[c]
All seizures	17	46	0.003[c]
Subject's global evaluation of improvement in seizure severity[d]	56	62	0.490[e] 0.388[f]

[a] A treatment responder is defined as subject whose seizure rate was reduced 50% or more during the double-blind phase.
[b] Topiramate vs. placebo; two factor (treatment and center) ANOVA on ranks.
[c] Topiramate vs. placebo; Cochran-Mantel-Haenszel test.
[d] Percent of subjects who had minimal, moderate, or marked improvement in seizure severity.
[e] Topiramate vs. placebo; Wilcoxon rank-sum test stratified by center.
[f] Topiramate vs. placebo; Wilcoxon rank-sum test unstratified.

When treatment responder was defined more rigorously as ≥75% seizure rate reduction for both PGTC and all seizures, the difference between topiramate (33% and 26%) and placebo (13% and 7%) was statistically significant ($p \leq 0.037$). The percentage of subjects who were seizure-free numerically favored topiramate (13% and 5%) over placebo (5% and 0%) for both PGTC seizures and all seizures, respectively. Sixty-two percent and 56% of topiramate and placebo subjects, respectively, reported improvement in seizure severity; the between-group difference in improvement in seizure severity was not statistically significant ($p=0.490$). Because plasma concentrations of concomitant AEDs were generally comparable over time between topiramate- and placebo-treated subjects, the topiramate effects observed in this study were not mediated through changes in plasma concentrations of concomitant AEDs. There was no consistent relationship between efficacy and plasma topiramate concentration.

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SAFETY RESULTS: Seasonal illnesses and associated symptoms were the most commonly reported treatment-emergent adverse events in both treatment groups in this trial. Neuropsychiatric adverse events were reported in both topiramate and placebo treatment groups in this trial. Anorexia, difficulty with memory, fatigue, nervousness, psychomotor slowing, somnolence, and speech disorders and related speech problems were reported more frequently for topiramate than for placebo. In comparison, insomnia, dizziness, headache, and personality disorder were reported more frequently for placebo than for topiramate (Table 2). In addition to these neuropsychiatric adverse events, differences between placebo and topiramate were also found for weight decrease (2%, placebo; 15%, topiramate) and injury (20%, placebo; 8%, topiramate). Overall, the neuropsychiatric treatment-emergent adverse event profile was milder compared to that previously reported for topiramate-treated adult subjects with partial onset seizures.

Table 2: Incidence of Common[a] Treatment-Emergent Neuropsychiatric Adverse Events
(All Randomized Subjects; Protocol CR005455)

	Placebo (N=41)		Topiramate (N=39)	
Preferred Term	No.	%	No.	%
Somnolence	6	15	10	26
Fatigue	3	7	7	18
Anorexia	3	7	6	15
Difficulty with memory	0	0	5	13
Headache	8	20	5	13
Dizziness	6	15	4	10
Nervousness	0	0	4	10
Psychomotor slowing	1	2	4	10
Speech disorders and related speech problems	1	2	4	10
Insomnia	5	12	1	3
Personality disorder	4	10	0	0

[a] Treatment-emergent neuropsychiatric adverse events reported by 10% or more subjects in either treatment group

No subject died during the trial or within 30 days of completion of the double-blind phase. Two subjects (one topiramate-treated and one placebo-treated) prematurely discontinued study medication and an additional six subjects (two placebo-treated and four topiramate-treated) had serious treatment-emergent adverse events.

Compared with placebo, topiramate had no effect on the subjects' mental status in terms of improvement in alertness, level of interaction with the environment, ability to perform the activities of daily living, and responsiveness to verbal requests.

No noteworthy hematologic, renal, or liver toxicity was observed (most of the few observed abnormalities were sporadic, transient, and did not lead to alteration in treatment). Except for mild changes in body weight, there were no noteworthy treatment-related changes in vital signs, ECGs, neurologic or physical examinations.

CONCLUSION: Topiramate was well-tolerated in this trial when administered to subjects with PGTC seizures. Topiramate was effective in reducing the rate of occurrence of PGTC seizures. Topiramate was also effective in reducing the rate of occurrence of all seizures.

Date of the report: 24 June 1997

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